REMARKS

I. Request for Continued Examination

A Final Action, dated March 17, 2009, was issued in the present application (Application No. 10/828,474). Applicants respectfully submit herewith a Request for Continued Examination (37 C. F.R. 1.1 14).

II. Status of the Claims

No claims have been amended, no claims have been canceled, and no claims have been added in the RCE submitted herewith. Claims 1-96 are pending and claims 1-8 are 68-73 under consideration in this application.

III. Elected and Examined Subject

The Office Action dated October 16, 2008 in the third paragraph, page 2 states, "claim 1 is partially directed to a species that is independent...". Is it the Examiner's position that only part of claim 1 is pending and has been searched, namely the part to the extent it reads upon formula III? Clarification is requested. Applicants requested the same clarification in their response of December 17, 2008, but did not receive an answer.

The Examiner is respectfully reminded of the procedure to be followed in election of species practice as stated in the MPEP §803.02 6th paragraph, "[s]hould applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The examination **will be extended** (emphasis added) to the extent necessary to determine patentability of the Markush-type claim." Applicants believe the arguments below overcome the obviousness rejection made by the Examiner. Thus, Applicants' request that examination be extended to encompass the remaining claimed compounds of formulas I, II, IV, and IV.

IV. Rejections of claims under 35 U.S.C. § 103(a)

Claims 1-8 and 68-73 remain rejected as obvious over Creemer ('906) in view of Gutman (Toxins and Signal Transduction) and Zhu ('547). Applicants still assume that

the rejection was intended to be over Creemer ('906) in view of Zhu ('547) with motivation supplied by Gutman (Toxins and Signal Transduction). Applicants also still assume the teaching of Zhu ('547) made in the Office Action dated October 16, 2008 was intended to be –O-(CO)-(CH_2)-S-(CH_2**CH_2**)-PEG- (emphasis added), otherwise the teaching would not fit Applicants' claims.

It is unclear which of the present claim limitations the Examiner thinks are taught or suggested by Gutman (Toxins and Signal Transduction). The Examiner states Gutman (Toxins and Signal Transduction) teaches the limited solubility and instability in water of wortmannin. Wortmannin as such, water solubility, and water stability are not limitations of the present claims. To the contrary, Applicants' compounds differ in structure from wortmannin, are soluble in water, and are stable in water. The teachings of Gutman (Toxins and Signal Transduction) do not teach or supply any part of the present claims.

Initially Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness. The MPEP in §2142-§2143 describes the legal concept and the Examiner's burden to establish the *prima facie* case.

The MPEP in §2143.02 requires the changes to be made to the prior art as urged by the Examiner must have a reasonable expectation of success . The MPEP states in Section II, "AT LEAST SOME DEGREE OF PREDICTABILITY IS REQUIRED; APPLICANTS MAY PRESENT EVIDENCE SHOWING THERE WAS NO REASONABLE EXPECTATION OF SUCCESS"

> "... at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)."

Applicants have previously submitted as evidence Greenwald (J. Controlled Release), which states, in then first sentence of the abstract, "[n]o low molecular weight (<20 000) poly(ethylene glycol) (PEG) small molecule drug conjugates, prepared over a 20-year period, have led to a clinically approved product." Applicants' formula III is a

small molecule drug conjugated to a 5000 molecular weight modified PEG. The molecular weight of Applicants' working example of formula III is found in lines 3-18, page 30. One reason for Greenwald (J. Controlled Release) to make the conclusion above is found in the paragraphs **2** and **3.1** spanning pages 160 to 161. **Conjugation of small molecule drugs with <20 000 PEG chains is art recognized to dramatically lower the *in vitro* activity and show no activity *in vivo*** (emphasis added). This evidence is found in sentences 2, 3, and the sentence spanning the two columns in paragraph **2**, page 160 of the reference. Greenwald (J. Controlled Release) in the last sentence paragraph 3.1, page 161 emphasizes, "the necessity for *in vivo* testing to verify *in vitro* cytotoxicity results".

Applicants now submit as additional evidence Bebbington (Bioorganic & Medicinal Chemistry Letters), Feng (Bioorganic & Medicinal Chemistry Letters), and Greenwald (Advanced Drug Delivery Reviews) and refer the Examiner to the passage in the specification spanning line 21, page 4 to line 12, page 5.

Bebbington (Bioorganic & Medicinal Chemistry Letters) in the first complete paragraph, left column, page 3298, teaches that adding a short PEG conjugate to iron-chelator molecule **1** gave conjugates with such low water solubility, they presumably could not be tested biologically. Feng (Bioorganic & Medicinal Chemistry Letters) teaches in Table 2, page 3302 that PEG of an unspecified molecular weight conjugated to a series of paclitaxel prodrugs produced compounds **5a-5f** with variable *in vitro* activity compared to paclitaxel itself, including some PEG conjugates with worse *in vitro* activity. For example, table 3, page 3303, teaches that PEG conjugate **5f**, which has the lowest IC_{50} at 96 hours of the six conjugates is far less efficacious, even at higher doses, *in vivo* than is paclitaxel. Greenwald (Advanced Drug Delivery Reviews), although partially cumulative to Greenwald (J. Controlled Release) discussed above, offers the additional evidence in the second complete paragraph, right column, page 220 that a PEG conjugate of molecular weight 5,000 of paclitaxel was a thousand times less active *in vitro* than paclitaxel itself. In the paragraph spanning the two columns of page 223, a different PEG conjugate of molecular weight 5,000 of paclitaxel is reported to equivalent to paclitaxel

in vitro again P388 cells but non-efficacious *in vivo*. Individually and is sum, the above-discussed references teach a low expectation of success using any low molecular weight PEG conjugated to a compound such as wortmannin.

By contrast to the predictions of Greenwald (J. Controlled Release), Bebbington (Bioorganic & Medicinal Chemistry Letters), Feng (Bioorganic & Medicinal Chemistry Letters), and Greenwald (Advanced Drug Delivery Reviews), Applicants' conjugated compounds show better activity in the *in vitro* Thymidine and MTS assays than does the unconjugated drug. This evidence is found on page 38 of the specification. Compound III without the water-soluble portion is 17-dihydrowortmannin. Even more striking are the *in vivo* results in the U87MG mouse xenograph model found on page 36. Applicants' conjugated compound III shows a lower tumor volume (44%) than does control. Applicants' conjugated compound III is even much better than the unconjugated drug (60% of control).

The Examiner in the paragraph spanning pages 2 to 3 of the Final Rejection mailed March 17, 2009 mistakenly assumes that the above argument is an unpredictability and teaching away argument and applies only to claims 3-8. Although the art taught away from and did not predict the present invention, the art suggested that the result was predictable. The state of the art prediction was that low molecular weight PEG conjugation does not work to make active compounds. There was no reasonable expectation of finding any *in vivo* activity of the compounds embraced by compound claims 1 and 68-73 and of finding any *in vivo* activity of the compositions embraced by claim 2 until Applicants did the experiments. The Examiner has never offered any evidence that any low molecular weight (<20,000) poly(ethylene glycol) (PEG) small molecule drug conjugate shows *in vivo* activity. Zhu ('547), the reference cited by the Examiner to supply –O-(CO)-(CH_2)-S-(CH_2CH_2)-PEG- limitation, has no *in vivo* data. In lines 56-65, column 9 of Zhu ('547) shows *in vitro* data for a 5,000 molecular weight PEG conjugate. The data are in weight, not concentration terms, but conclude the conjugated and non-conjugated compounds are "equivalent" *in vitro*, not improved by conjugation. Thus, based on the evidence proved by Applicants, there is no reasonable

expectation of finding any *in vivo* activity in a low molecular weight PEG small molecule conjugate.

As evidenced by Holleran (Drug Metab Dispos) in the last paragraph, page 492, the solubility of wortmannin in water is 300 μM. This is far above the 5 nM IC_{50} for PI3K inhibition, which is the mechanism of action of wortmannin. At a concentration of 100 nM, (0.03% of its maximum solubility in water), wortmannin inhibits 95% of the PI3K binding site. This evidence is found in the paragraph spanning pages 3269 to 3270 of Ng (Clin. Cancer Res.). Increasing the water solubility of wortmannin was not the motivation for preparing the conjugates of the present application. In fact, there is no need to increase the water solubility, since wortmannin's solubility exceeds its IC_{50} by a factor of 60,000. Since a saturated water solution of wortmannin will inhibit 99.9999+% of the PI3K sites to which it is exposed, there would be no practical pharmacological effect to somehow doubling wortmannin's available concentration. When the vast majority of sites are blocked, there is no physiological effect of blocking an additional 0.00001% of the sites. Using the molecular weight of 428.44 for wortmannin, one can easily calculate that the water solubility of wortmannin is about 130 μg/ml. The solubility of rapamycin, the compound modified by Zhu ('547), is about 1 μg/ml. This is 130 times less than the solubility of wortmannin. The MPEP §2143 C states that "Use of Known Technique To Improve Similar Devices (Methods, or Products) in the Same Way" is a way to establish a *prima facie* case of obviousness. However, that does not apply here since the problem solved by Zhu ('547), the lack of water solubility of rapamycin, is not the problem to be solved with wortmannin, which has sufficient water solubility but suffers from other problems.

The Examiner in lines 6-10, page 3 of the Final Rejection mailed March 17, 2009 mistakenly states that the solubility of the compounds rapamycin and wortmannin "are not at issue" and erroneously concludes that the problem to be overcome in making wortmannin into an effective drug is its "limited solubility". The specific values of the two solubilities are facts, not at issue, but the meaning of those values, the teachings of

Gutman (Toxins and Signal Transduction), and the nature of the problem to be overcome are presently in dispute.

The Examiner supplied only one of the twenty-nine pages of the reference he calls Gutman (Toxins and Signal Transduction). The Applicants now supply the complete reference, to which they refer as Whalin (Toxins and Signal Transduction). Whalin (Toxins and Signal Transduction) teaches, "limited solubility" of wortmannin in the third complete paragraph of page 429. This statement in Whalin (Toxins and Signal Transduction) is purely conclusional, since there is neither any data cited in support of this conclusion nor any context describing how soluble a compound must be to achieve *in vivo* activity. The analysis above, not rebutted by the Examiner, proves that the water solubility of wortmannin is not the cause of its lack of *in vivo* efficacy.

Since "limited" is a relative term, what does that mean in practical terms? The Applicants agree that wortmannin is less soluble in water than, -say, sugar. However, the analysis above shows that wortmannin is soluble enough to completely block PI3K under physiological conditions. That is not the case with rapamycin, the compound used by Zhu ('547). As shown in lines 1-6, page 4 of the specification, the problem to be solved is the lack of *in vivo* activity of wortmannin derivates, even when *in vitro* potency exists. The MPEP §2143.01 requires there be some "suggestion or motivation modify the references" to establish a *prima facie* case of obviousness. Since the solubility of wortmannin in water is not the problem to be solved, Gutman (Toxins and Signal Transduction) fails to provide any motivation to combine the references Creemer ('906) and Zhu ('547).

The MPEP §2141.02 pertains to "[a]scertaining the differences between the prior art and the claims at issue". Creemer ('906) does not teach the wortmannin core with R_2 = phenyl as stated by the Examiner in the Office Action dated October 16, 2008. The Examiner clarified in lines 11-16, page 3 of the Final rejection mailed March 17, 2009 that the molecule upon which he is basing the obviousness rejection is wortmannin itself, found in lines 10-30, column 1 of the reference, not to compound (j). Wortmannin has a carbonyl group at position 17. Applicants' formula III requires that this carbon atom be

reduced to the alcohol oxidation state. Applicants' formula III has a –O-(CO)-(CH_2)-S- linking group attached to the oxygen atom at position 17. Applicants' formula III has a PEG chain attached to that linking group. This is a third difference between wortmannin taught by Creemer ('906) and Applicants' formula III. This is not the usual ethyl *versus* methyl obviousness situation of MPEP §2144.09.

Nowhere does Creemer ('906) teach the reduction of wortmannin to 17-dihydrowortmannin, although in Scheme II, bridging columns 9-12, the reference does teach the reduction of 11-propionyl wortmannin (g) to the 17-dihydro compound (e). Converting compound (e) of Creemer ('906) to Applicants' formula III, would require yet more steps of removing the 11-propionyl group and replacing it by Applicants' claimed 11-acetyl group. Arguably this is a fourth degree of separation between the teachings of Creemer ('906) and Applicants' formula III.

The Examiner in the Final Rejection mailed March 17, 2009 did not address the many changes required to convert wortmannin into Applicants' formula III, except to acknowledge they exist. In two post-KSR cases, the Court of Appeals for the Federal Circuit has rendered decisions in which the obviousness of a chemical compound was at issue. In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, a prior art reference teaching a compound with a methyl group at position 6 on a pyridyl ring did not make obvious a claimed compound with an ethyl group at position 5 on its pyridyl ring. In *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 533 F.3d 1353 a prior art compound having a trifluoroethoxy at the 4-position on a pyridine ring did not make obvious a compound with a methoxypropoxy substituent at the same place. These are compounds much closer in structure than wortmannin and Applicants' formula III and requiring fewer changes than those urged by the Examiner. Yet, the Court of Appeals for the Federal Circuit held them not to be obvious.

Zhu ('547) teaches a derivative of rapamycin called SDZ-RAD conjugated with the –O-(CO)-(CH_2)-S-($CH_2CH_2O)_n$-CH_3 radical where n is 5-450 in lines 1-17, column 3. Rapamycin is a macrocyclic lactone with a twenty-nine membered central ring. Applicants' formula III has a furanosteroid with five fused six- and five-membered rings.

Zhu ('547) teaches conjugation through a primary alcohol. Applicants' formula III is conjugated through a secondary alcohol. The rapamycin core taught by Zhu ('547) contains nitrogen. Applicants' formula III does not.

Rapamycin, which forms the core of Zhu's ('547) teaching, according to Wikipedia, "bind[s] the cytosolic protein FK-binding protein 12 (FKBP12) in a manner similar to tacrolimus. However, unlike the tacrolimus-FKBP12 complex, which inhibits calcineurin (PP2B), the [rapamycin]-FKBP12 complex inhibits the mammalian target of rapamycin (mTOR) pathway by directly binding the mTOR Complex1 (mTORC1). mTOR is also called FRAP (FKBP-rapamycin associated protein) or RAFT (rapamycin and FKBP target). The IC_{50} for the inhibition of mTOR activity by rapamycin alone is 77,000 nM while the IC_{50} for rapamycin + FKBP 12 is 56 nM."

By contrast wortmannin, used to make Applicants' formula III, is according to Wikipedia, "a specific, covalent inhibitor of phosphoinositide 3-kinases (PI3Ks). [Wortmannin] has an *in vitro* inhibitory concentration (IC_{50}) of around 5 nM, making it a more potent inhibitor than LY294002, another commonly used PI3K inhibitor. [Wortmannin] displays a similar potency *in vitro* for the class I, II, and III PI3K members although it can also inhibit other PI3K-related enzymes such as mTOR, DNA-PK, some phosphatidylinositol 4-kinases, myosin light chain kinase (MLCK) and mitogen-activated protein kinase (MAPK) at high concentrations. Wortmannin has also been reported to inhibit members of the polo-like kinase family with IC_{50} in the same range as for PI3K." Wortmannin has an *in vitro* inhibitory concentration (IC_{50}) of around 730 nM against mTOR, which is only 0.7% of its potency against PI3K. Wortmannin is a biochemical tool, not used clinically. Rapamycin has demonstrated anticancer effects in humans. The MPEP §2141.01(a) I. requires that "TO RELY ON A REFERENCE UNDER 35 U.S.C. 103, IT MUST BE ANALOGOUS PRIOR ART". Wortmannin and rapamycin are simply different compounds with different mechanisms of action. They are not in analogous arts.

The Examiner in the Final Rejection mailed March 17, 2009 in the paragraph spanning pages 3 to 4, uses form paragraph 7.37.13 to state that Applicants are attacking

the references individually. In fact, that would always be true when discussing more than one reference, but here Applicants are arguing that the references don't say exactly what the Examiner says they say, have no motivation to be combined, are in non-analogous fields, and if combined would be expected to produce compounds not active *in vivo*.

The MPEP §2141 III. (E) states that a conclusion of obviousness can be supported by a rationale of, "[o]bvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success". In line 11, page 8 of the Office Action of October 16, 2008, the Examiner states "Zhu et al teaches the use of the of the conjugate ester –O-(CO)-(CH2)-S-(CH2)-PEG- as a means of increasing the solubility of otherwise insoluble compound (column 3 lines 18-32)". In fact, Zhu ('547) teaches conjugation of only two compounds, SDZ-RAD and rapamycin, not all water insoluble compounds and not all compounds with known *in vitro* anti-proliferation activity. The number of compounds, like wortmannin, which are reported in the literature to inhibit tumor cell growth *in vitro* probably numbers in the hundreds of thousands, possibly millions. The number of distinct methods used by medicinal chemists to increase water solubility or *in vivo* activity by structural modification is probably large. Does the Examiner argue that attachment of the side-chain pictured at position 17 in Applicants' formula III to any or all of these millions of compounds of diverse structure is obvious? There are twenty-three carbon atoms in wortmannin. Two of these carbons C-10 and C-13 are quaternary and probably immune from modification. Some synthetic process to attach the –O-(CO)-(CH_2) -S- (CH_2) -PEG- side chain probably could modify the remaining twenty-one. Why choose C-17 to make Applicants' compound III? Where is the teaching to make this compound alone? Why attach the –O-(CO)-(CH_2)-S-(CH_2)-PEG- side chain and not some other property-altering side chain? Such a conclusion is not supported by the requirement that the number of solutions be finite and predicted to lead to a positive result.

The Examiner in the Final Rejection mailed March 17, 2009 in lines 3-8, page 4 states that "an infinite number of compounds and possibilities" were not cited in the prior office action. Applicants never used the word infinite, rather used the word millions.

The phrase "finite number" in MPEP §2141 III. (E) should not be interpreted in the way used by the mathematician Georg Cantor to mean "not without end", but rather as "not a large number".

Secondly, although Applicants believe the Examiner has failed to make a *prima facie* case of obviousness, under the guidance of MPEP §2144.09 VII., and MPEP §2145 X D. 2. Applicants argue that "superior or unexpected results" exist, that the secondary consideration of a long-felt but unsolved need exists, and that the references used to make the obviousness rejection teach away from the combination urged by the Examiner. Applicants' unexpected results argument will focus on *in vivo* data. Whalin (Toxins and Signal Transduction) comments that, "caution should be used in interpreting the cellular effects of [wortmannin], because its effective concentration varies depending on the experimental conditions, such as time, temperature, pH, cell line used, concentration of protein, and cell density". A head-to-head comparison between wortmannin and Applicants' compound, exists for toxicity. Schultz (Anticancer Res.) reports that wortmannin has a maximally tolerated dose, defined as the LD_{20}, of 0.38 to 0.75 mg/kg *p.o.* in the mouse, depending upon which tumor cell line is used. The minimum effective dose against C3H and BxPC3 is approximately 0.9 and 0.38 mg/kg respectively, which would be 70% and 50% of the maximally tolerated dose. Schultz (Anticancer Res.) also reports a LD_{100} of 1.5 mg/kg, with the understated comment this is "an extremely sharp dose response for toxicity".

Yu (Cancer Biology & Therapy) reports that the maximally tolerated dose of Applicants' formula III (PWT-458) is 15 mg/kg *i.p.* in the mouse in the U87MG human tumor xenograph model. Maximally tolerated dose is not defined in the paper but is also the LD_{20}. A dose of 20 mg/kg *i.p.* of Applicants' formula III in the mouse was used in the A549 tumor model, which one may infer was not totally fatal to the mice.

Yu (Cancer Biology & Therapy) in the first complete paragraph on page 541 reports that the minimally effective dose of Applicants' formula III (PWT-458) is 0.5 mg/kg *i.p.* in the mouse in the U87MG tumor xenograph model. The ratio between the maximally tolerated dose and the minimally effective dose in this model is 30. In the same paragraph the maximally tolerated dose and the minimally effective dose of 17-β

hydroxywortmannin are reported as 1.5 mg/kg *i.p.* and between 1.0 and 0.5 mg/kg *i.p* in the mouse in the U87MG human tumor xenograph model. The ratio between the maximally tolerated dose and the minimally effective dose for 17-β hydroxywortmannin in this same model is about 2. This ratio, known as the therapeutic window or therapeutic index, is unexpectedly higher for Applicants' formula III (PWT-458) compared to both wortmannin and 17-β hydroxywortmannin. Samuels (Cancer Biology & Therapy), in a commentary upon Yu (Cancer Biology & Therapy) states in the first complete sentence on page 547 that this result is, "a superior therapeutic index" over 17-β hydroxywortmannin.

Yu (Cancer Biology & Therapy) in the second complete paragraph on page 541 teaches that the therapeutic window (or index) of Applicants' formula III in the A549 human tumor xenograph model is "at least 10". As discussed above Schultz (Anticancer Res.) reports a therapeutic index for wortmannin of 1.4 and 2 in two different tumor xenograph models, the mouse C3H tumor and the human BxPC3 tumor, respectively. While these are not the same cell lines, the difference in therapeutic ratio between Applicants' formula III and wortmannin can only be characterized as unexpected.

Sato (J. Pharmacology. Exp. Ther.) reports on page 546, second paragraph that 17-β hydroxywortmannin, which they call LY301497, "rats did not survive 5 weeks of oral dosing of LY301497 at 1 mg/kg (100% mortality)."

Schultz (Anticancer Res.) reports *in vivo* data for wortmannin in seven mouse tumor xenograph models (C6, 6C3HED, C3H, B16, Lewis, M5, and X5563) and in ten human tumor xenograph models (MX1, CX1, GC3, HC1, VRC5, LX1, IGROV1, MIA PaCa2, PANC1, and BxPC3). Schultz (Anticancer Res.) concludes that wortmannin was effective against only two of the seventeen tumor xenograph models he tried, the mouse C3H tumor and the human BxPC3 tumor. Schultz (Anticancer Res.) mentions, "the limited antitumor activity of wortmannin", in his concluding sentence on page 1138.

Even more striking are the *in vivo* results in the U87MG human xenograph model found on page 36. Applicants' conjugated compound III shows a lower tumor volume (44%) than does control. Applicants' conjugated compound III is even much better than the unconjugated drug (60% of control). The expectation, again as discussed above, is

that adding the –O-(CO)-(CH_2)-S-(CH_2)-PEG- side chain to reduced wortmannin would reduce, not increase the *in vitro* activity and destroy, not increase the *in vivo* activity. Yu (Cancer Biology & Therapy) reports *in vivo* data for formula III (PWT-458) in three human tumor xenograph models (U87MG, A549, and A498), all of which we active.

Ng (Clin. Cancer Res.) reports on page 3273 that wortmannin failed to inhibit tumor growth at 0.35 mg/kg *i.p.* in the mouse in the PK1 human pancreatic tumor xenograph model. Norman (J. Med. Chem.) is largely cumulative to Schultz (Anticancer Res.) but does have additional data on wortmannin in the ovarian tumor xenograph model M5076, which it failed to inhibit. Norman (J. Med. Chem.) concludes, "[a] relationship also exists between *in vitro* potency and toxicity. The most potent PI 3-kinase inhibitors show toxicity at the lowest doses." That is not true of Applicants' compound, which does not show toxicity at the lowest dose and therefore is an unexpected result. Norman (J. Med. Chem.) also states, "[t]he narrow therapeutic index has made *in vivo* evaluation difficult for wortmannin and related analogs". Applicants' formula III does not have a narrow therapeutic index. Norman (J. Med. Chem.) also reports that 17-β hydroxywortmannin, did not inhibit tumor growth at 0.5 mg/kg *p.o.* in the mouse tumor xenograph model C3H, and was toxic at 1.0 mg/kg. That is about as bad a therapeutic index as one might fear.

As discussed above, Applicants' conjugated compounds show better activity in the *in vitro* Thymidine and MTS assays than does the unconjugated compound from which they were made. This evidence is found on page 38 of the specification.

As pointed out in lines 12-20, page 4 of the specification, reduced wortmannin derivatives acetylated at the C-17 hydroxyl group show a dramatic loss in activity. Two years after the filing date of Creemer ('906), Inventor Creemer (J. Med. Chem.) in a paper analyzing the structure-activity relationships among his compounds concluded, "the active site cannot accommodate lipophilicity or steric bulk at C-17". This evidence is found in the last two sentences, second paragraph, page 5022 of the reference. The conclusion is based the data for compounds **6-8** in Table 1 on the same page. Reducing the carbonyl group of 11-propionyl wortmannin to the alcohol gives a compound with about the same *in vitro* activity in the two assays as the ketone. Acylation of that alcohol

reduces the activity by 149 and 16 fold respectively in the two assays. Some of the same data are found in column 14, lines 36-40 of Creemer ('906) but without any conclusions. Applicants' formula III is acylated at C-17. The *in vitro* data from page 38 of the specification showing a 3-fold increase in activity rather than the decrease taught by Creemer (J. Med. Chem.), is on its face a completely unexpected result and contrary to the conventional wisdom in the art.

Wortmannin was first isolated in 1957. United States Patent Number 5,378,725, issued January 3, 1995, first disclosed that wortmannin inhibited PI 3-kinase in mammals. The passage in the specification spanning line 21, page 3 to line 20, page 4 gives some of the history of the many efforts to make a drug with *in vivo* activity from the wortmannin core. None of these efforts succeeded until Applicants' present formula III was made and tested. This is evidence that a long felt but unsolved need existed in the art of wortmannin pharmacology.

Whalin (Toxins and Signal Transduction) teaches, "[wortmannin] was identified as the hemorrhagic mycotoxin. It is a sterol-like compound that causes toxic effects in rats, including hemorrhages in the stomach, intestines, heart, and thymus" also in the third complete paragraph of page 429. In the first two lines of page 443, the reference teaches, "[wortmannin] binds covalently to the 110 kDa subunit of PI 3-kinase and irreversibly inhibits the enzyme". The teaching that wortmannin is both toxic and an irreversible inhibitor of its target enzyme teaches away using wortmannin as the starting point for a new compound synthesis program,

V. Period for Reply

The Final Rejection set a three-month period to comply, to and including June 17, 2009. On September 17, 2009, Applicants filed a notice of Appeal and purchased three additional months to reply, at that time. Since this reply is filed within two months from September 17, 2009, this response is believed to be timely filed. Should any additional fees be deemed necessary, Commissioner is authorized to charge Deposit Account No. 01-1425.

VI. Conclusion

It is Applicants' belief that claims 1-8 are 68-73 are in condition for allowance, and action towards that effect is respectfully requested. If there are any matters which may be resolved or clarified through a telephone interview, the Examiner is requested to contact the undersigned Agent at the number indicated. If the arguments presented above are not, in part, persuasive, then Applicants request a first action Final Rejection, so Applicants can prepare their Appeal Brief.

Respectfully submitted,

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